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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,507	01/23/2004	Bruce R. Line	Franco-Line Microprtcles	5234

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JUNEAU PARTNERS
P.O. BOX 2516
ALEXANDRIA, VA 22301

EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
07/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,507	LINE ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8,11-71 and 82-86* is/are pending in the application.

4a) Of the above claim(s) *27,28,41-71 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,11-26,29-40,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 4/17/2009, in reply to the Office Action mailed 8/6/2008, is acknowledged and has been entered. Claims 1,7,8,11-26, 29-35, 85 and 86 have been amended. Claims 2-6, 9,10, 72-81 have been cancelled. 1, 7, 8 and 11-71 and 82-86, are pending, of which claims 27, 28, 41-71 and 82-84 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 7, 8, 11-26, 29-40, 85 and 86 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection. Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7, 8, 11, 12, 16, 17, 30-36, 38,39, 40, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns *et al.* (US 7,276,254) in view of Schwarz (US 2004/0197264).

Burns discloses polymeric microspheres for biomedical applications having a biomedical functional material attached thereto, and an average particle diameter from about 1 to about 15 microns. The biofunctional material may be a radioactive material (abstract). The particles may also range in size from about 0.5 to about 20 microns (column 5, line 5). Any suitable polymer may be used to form the microspheres, for example polyesters, polyacrylate, polymethacrylate, etc. (column 5, lines 15 – 65). The particles may be subjected to optional surface treatment in order to attach or alter functional groups present on the surface of the microspheres (column 15, lines 40 – 50). Functional groups can be reacted with materials that may in turn act as linkages to biological materials, ligands (column 16, lines 38 – 50). Biological or medical materials can be attached to the surface of the microspheres by covalent bonding, complexation, adsorption and the like (column 19, lines 4 – 6). In a preferred embodiment, the radioactive constituent is chosen that so when administered, the radioactive

microspheres emit a therapeutic intensity and amount of short-range beta or gamma radiation, but will not emit a significant amount of unwanted beta or gamma radiation (column 19, lines 18 – 26). Yttrium and/or phosphorous may be incorporated into the microspheres (column 19, lines 33 – 63). Regarding claims 31 and 32, it is noted that the functional recitation that the particle has the claimed density range is not given patentable weight to distinguish over Burns. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Since Burns discloses microspheres comprising the same polymers as those claimed, they would inherently be capable of having the same density.

Burns does not specifically recite combination therapeutic and diagnostic microparticles comprising at least two radioactive therapeutic selected from therapeutic beta-emitting radionuclides and an imaging or diagnostic gamma-emitting radionuclide.

However, combination radiotherapy/diagnostic agents are known in the art, as shown by Schwarz.

Schwarz discloses microspheres impregnated with a radioisotope that emits therapeutic beta particles and a radioisotope that emits diagnostic gamma radiation; wherein the atomic number of the first radioisotope is not the same as the atomic number of the second radioisotope. In one preferred embodiment, the microsphere is

composed of glass impregnated with ^{90}Y as the source of the therapeutic and ^{198}Au as the source of diagnostic gammma emission (abstract). Suitable diagnostic radionuclides also include ^{99m}Tc (paragraph 0023). Suitable microspheres include glass, polymer, etc. (claim 1), including particle size 20-50 micrometers (claim 10), and density 1-4 g/cm^3 (claim 14).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a diagnostic imaging agent in combination with therapeutic yttrium-90 in the microspheres of Burns when the teaching of Burns is taken in view of Schwarz. Schwarz teaches that the development of microspheres for radionuclide therapy is complicated by the difficulty in determining the biodistribution of the microspheres in vivo, which is critically important because the microsphere must be close in proximity to the tumor being treated, and that a solution to this problem is to attach a detectable non-hazardous signal (paragraph 0008). Therefore, one of ordinary skill would have been motivated to provide a beta-emmiting radionuclide such as 198Au, 99mTc, etc. in the microparticles of Burns for the purpose of monitoring biodistribution, as was shown by Schwarz.

With regard to Burns, Applicant argues on pages 12-13 of the Response that Burns does not disclose a diagnostic, and that it "appears that Burns may disclose water-swellable polymers." This is not found to be persuasive. Burns is not limited to water-swellable polymers.

Claims 1, 7, 8, 11-26, 29-40, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns *et al.* (US 7,276,254) and Schwarz (US 2004/0197264), in view of Wu *et al.*(Bioorg. Med. Chem. Lett., 1994, 4, p. 449-454), in further view of Danthi *et al.* (US 2003/0133972) and Lugade *et al.* (US 7,241,883).

Burns discloses polymeric microspheres for biomedical applications, as set forth above. The particles may be subjected to optional surface treatment in order to attach or alter functional groups present on the surface of the microspheres (column 15, lines 40 – 50). Functional groups can be reacted with materials that may in turn act as linkages to biological materials, ligands (column 16, lines 38 – 50). Biological or medical materials can be attached to the surface of the microspheres by covalent bonding, complexation, adsorption and the like (column 19, lines 4 – 6). In a preferred embodiment, the radioactive constituent is chosen that so when administered, the radioactive microspheres emit a therapeutic intensity and amount of short-range beta or gamma radiation, but will not emit a significant amount of unwanted beta or gamma radiation (column 19, lines 18 – 26). Yttrium and/or phosphorous may be incorporated into the microspheres (column 19, lines 33 – 63).

Burns does not recite combination radiotherapy/imaging, and fails to specifically recite the identity of the moiety which may be employed to provide linkage, covalent bonding, complexation of the biological material, e.g. radioactive constituent, onto the microsphere.

Schwarz discloses microspheres impregnated with a radioisotope that emits therapeutic beta particles and a radioisotope that emits diagnostic gamma radiation;

wherein the atomic number of the first radioisotope is not the same as the atomic number of the second radioisotope. In one preferred embodiment, the microsphere is composed of glass impregnated with ^{90}Y as the source of the therapeutic and ^{198}Au as the source of diagnostic gammma emission (abstract). Suitable diagnostic radionuclides also include ^{99m}Tc (paragraph 0023). Suitable microspheres include glass, polymer, etc. (claim 1), including particle size 20-50 micrometers (claim 10), and density 1-4 g/cm^3 (claim 14).

Wu discloses polyamidoamine dendrimers modified to chemically react with DOTA and DTPA type bifunctional metal chelators and coupled to monoclonal antibody. DTPA and DOTA-dendrimer-antibody constructs were easily labeled with ^{90}Y, ^{111}In, ^{212}Bi, suggesting use of the constructs for use in mAB guided radiotherapy or imaging (abstract).

Wu teaches dendrimer-DOTA-^{90}Y conjugated to antibody, rather than microsphere. However, the use of dendrimer as a linking agent for conjugation to microsphere is known in the art, as shown by Danthi and Lugade.

Danthi discloses that dendrimers can be readily used as linking carriers by employing a variety of chemical conjugation techniques to attach the targeting entity and therapeutic entity. For example, a dendrimer having a disulfide (--S--S--) bond in its core. The final external layer of the dendrimer can be capped with a reactive group such as an amine or carboxyl group. These reactive groups can then be derivatized with either targeting entities or therapeutic entities (or, in some cases, a mixture of both). The core disulfide bond can then be reduced to a thiol, and the complementary

entity attached via the thiol functionality. That is, if a therapeutic entity had been attached to the external layer of the dendrimeric linking carrier, upon reduction and formation of the thiol functionality, a targeting entity can be attached via the free --SH group (paragraph 0120 – 0122).

Lugade also discloses that dendrimers are useful linkers by which to attach functional groups to microsphers (see column 10, lines 5 – 31).

It would have been obvious to one having ordinary skill in the art at the time of the instant invention to provide the radioactive yttrium constiutent of Burns in the form of a dendrimer-linked DOTA or DTPA carrier when the teachings of Burns are taken in view of Danthi, Lugade and Wu. Burns does not specifically teach the identity of the moiety which is used to introduce the radioactive constituent (e.g. yttrium), thus one of ordinary skill in the art would have been motivated to seek out a suitable moiety which would be capable of linking, covalent bonding, complexation onto the microsphere for radiotherapy. Dendrimer-conjugated DOTA or DTPA are known in the art to be a suitable carrier for radioactive yttrium, as shown by Wu. Wu discloses dendrimer-DOTA-^{90}Y (and other radionuclides) for the purposes of radiotherapy and imaging, but does not teach their conjugation to microsphere. However, dendrimer is known to be a suitable linking moiety to conjugate a functional group to microsphere as shown by Danthi and Lugade. It would have been obvious to one of ordinary skill to utilize such a dendrimer-DOTA conjugate to introduce radioactive yttrium to the microspheres of Burns by application to the formed microspheres, and one would have had a reasonable expectation of success in doing so, because Burns teaches radioactive yttrium to be

useful when incorporated onto microspheres for emitting radiation that will spare healthy tissue remote from the tumor site in which the microsphere is embedded (column 19, lines 8 - 64) and because Wu teaches dendrimer-DOTA as a successful carrier for ^{90}Y for radiotherapy/imaging. It would have been further obvious to one of ordinary skill in the art at the time of the invention to provide a diagnostic imaging agent in combination with therapeutic yttrium-90 in the microspheres of Burns when the teaching of Burns is taken in view of Schwarz. Schwarz teaches that the development of microspheres for radionuclide therapy is complicated by the difficulty in determining the biodistribution of the microspheres in vivo, which is critically important because the microsphere must be close in proximity to the tumor being treated, and that a solution to this problem is to attach a detectable non-hazardous signal (paragraph 0008). Therefore, one of ordinary skill would have been motivated to provide a beta-emmiting radionuclide such as 198Au, 99mTc, etc. in the microparticles of Burns for the purpose of monitoring biodistribution, as was shown by Schwarz.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS